Landfill Disposal as an Approach to Reduce Discharges of Medicines from POTWs

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ABSTRACT

The Pharmaceutical Research and Manufacturers of America (PhRMA) initiated research in 1999 to evaluate the pathways and fate of active pharmaceutical ingredients from the consumer to surface waters. One potential pathway identified by PhRMA is the disposal of unused pharmaceutical products that are discarded by consumers in household trash and disposed of in municipal solid waste landfills. PhRMA initiated this study to evaluate surface water exposures through the landfill disposal pathway.

The estimated releases to surface water of 24 example active pharmaceutical ingredients (APIs) in landfill leachate were calculated for three assumed disposal scenarios: 5%, 10%, and 15% of the total annual quantity of API sold is discarded unused. The estimated releases from landfills to surface waters, after treatment of the leachate, were compared to the total amount of each example API that would be released to surface waters from publicly owned treatment works, generated by patient use and excretion.

KEYWORDS: Pharmaceuticals, unused medicines, landfills, landfill leachate, POTW discharges, surface water discharges.

INTRODUCTION

The detection of trace concentrations of human pharmaceutical compounds in surface water and ground water continues to receive considerable attention in the technical literature and popular press. The improved precision and accuracy of analytical methods for trace organic chemicals, which includes pharmaceutical products and many other types of consumer products, has led to concerns about potential exposure of humans to these chemicals through the drinking water pathway and to aquatic biota that are in surface waters that receive treated domestic sewage. The Pharmaceutical Research and Manufacturers of America (PhRMA) initiated research in 1999 to evaluate the pathways and fate of active pharmaceutical ingredients from the consumer to surface waters. Potential pathways identified by PhRMA are the disposal of unused pharmaceutical products by consumers in household trash that is disposed of in municipal solid waste (MSW) landfills and flushing unused medicines directly to public sewerage systems. This study compares the relative contributions to the total mass of medicines found in the environment from patient dosing with the mass that results from landfill disposal and from flushing of unused medicines. The definition of unused medicines in this study is limited to unused products that are disposed of by patients. Only the active pharmaceutical ingredients (API) in prescription and generic drugs are evaluated in this study. Bulk quantities, surplus, or expired APIs generated by wholesalers or pharmacies are specifically excluded from this analysis because they are returned to their manufacturers and are generally not discarded in municipal landfills. Only landfills defined and regulated as MSW landfills by Subtitle D of the Resources Conservation and Recovery Act (RCRA) are evaluated in this study.

The research compares the API releases in treated landfill leachate to the environmental loadings to surface waters from patient use of pharmaceutical products. In addition, an evaluation of the relative contribution of medicines to surface water based on an assumed scenario where all unused medicines are disposed of by flushing to municipal sewerage systems is presented.

METHODOLOGY

Scope

This study evaluated the potential releases of APIs to surface water in landfill leachate, assuming a range of amounts of unused pharmaceuticals discarded by consumers. The annual amounts of APIs sold were obtained from IMS Health Inc. The quantities of APIs released in landfill leachate are calculated using a partitioning coefficient and account for anaerobic biodegradation and hydrolysis of the APIs in a landfill. The estimates of potential API releases to surface waters account for the collection and treatment of the landfill leachate at publicly owned treatment works (POTW) and privately-owned treatment plants that comply with the U.S. Environmental Protection Agency's (EPA) effluent limitations guidelines for Subtitle D landfills (40 CFR 445, Subpart B). The estimated releases from POTWs due to patient use and excretion

Example Active Pharmaceutical Ingredients

Twenty-three APIs that represent a range of prescription drugs in terms of sales and physical-chemical properties were chosen for this evaluation because these APIs were included in the 2002 U.S. Geological Survey (USGS) study of APIs and consumer products in U.S. surface waters (Kolpin, D.W., et. al., 2002). One API metabolite, paroxetine hydrochloride, was also included in the USGS survey and is included in this evaluation. It is considered to be an API for the purposes of this report, which results in a total of 24 example APIs for this study. Table 1 lists the 24 example APIs evaluated in this study and includes their CAS numbers, molecular weights, and the mass of each sold annually. An adjustment factor to convert mass of salt to mass of active ingredient is also shown in Table 1. Salt forms of APIs are often used in formulations because of their stability and other favorable physical properties. However, upon ingestion and/or entry into the aquatic environment, the salts will dissociate into their acid or base forms and their behaviors and effects will be a function of those forms. A mass adjustment factor is required to convert the mass volume of the formulated salt into the mass volume of the moiety actually present in the environment.

Table 1. Annual U.S. Sales Data for APIs Evaluated

Substance	CAS	Molecular Wt.	Mass Volume Adjustment Factor	Mass of API-salt Qt (kg/yr)	Mass of API Qt (kg/yr)
Acetaminophen	103-90-2	151.16	1		5691120
Albuterol (salbutamol)	18559-94-9	239.31		4300	
Sulfate (2:1)	51022-70-9	576.7	0.83		3569
Cimetidine	51481-61-9	252.34		57448	
Hydrochloride	70059-30-2	288.81	0.87		49980
Ciprofloxacin	85721-33-1	331.35		94933	
Hydrochloride	86393-32-0	367.81	0.9		85440
Codeine	76-57-3	299.37		20127	
Phosphate	52-28-8	397.36	0.75		15095
Sulfate	6854-40-6	397.45	0.75		
Digoxin	20830-75-5	780.95	1		229
Diltiazem	42399-41-7	414.52		162278	
Hydrochloride	33286-22-5	450.98	0.92		149296
Doxycycline	564-25-0	444.44		38121	
Hyclate (HCl, ½ C_2H_6O, ½ H_2O)	24390-14-5	512.9	0.86		32784
Enalapril	75847-73-3	376.45		1087	
Maleate	76095-16-4	492.52			
Enalaprilat	76420-72-9	348.4	0.71		772
Erythromycin	114-07-8	733.93		65595	
H_2O		751.94	0.98		64283
Fluoxetine	54910-89-3	309.33		13971	
Hydrochloride	56296-78-7	345.79	0.89		12434
Gemfibrozil	25812-30-0	250.34	1		231530
Ibuprofen	15687-27-1	206.28	1		1035229
Lincomycin	154-21-2	406.54		357	
Hydrochloride	859-18-7	443	0.92		328
Metformin	657-24-9	129.17		2048573	
Hydrochloride	1115-70-4	165.63	0.78		1597887
Norfloxacin	70458-96-7	319.33	1		2700
Oxytetracycline	79-57-2	460.44		34	
Hydrochloride	2058-46-0	496.9	0.92		31
Paroxetine	61869-08-7	329.37		21400	
Hydrochloride	78246-49-8	365.83			
Metabolite		331.38	0.91		19474
Ranitidine	66357-35-5	314.41		111574	
Hydrochloride	71130-06-8	350.87	0.9		100417
Sulfamethoxazole	723-46-6	253.28	1		314389
Sulfathiazole	72-14-0	255.32	1		483
Tetracycline	60-54-8	444.44		74532	
Hydrochloride	64-75-5	480.9	0.92		68569
Trimethoprim	738-70-5	290.32	1		64450
Warfarin	5543-58-8	308.33		4300	
Sodium		331.32	0.93		3999

Partitioning Coefficients

Solids/liquid partition (adsorption) coefficients are used to predict the extent to which an organic chemical partitions between the solid and solution phases of water and soils, sediments, and other solids including the organic solid wastes in landfills (Lyman, W.J., et al., 1990). The water-organic carbon partitioning coefficient (K_{OC}) and the octanol-water partition coefficient (K_{OW}) of a specific organic chemical are both measures of its hydrophobic characteristics and are used as surrogates to estimate the chemical's potential to partition to solids.

The ability to estimate the sorption of an API to solids in various media is critical to understanding its environmental fate. Unfortunately, many of the methodologies and relationships used for determining this important parameter, like K_{OW}, were derived from

studies with neutral, hydrophobic compounds such as pesticides and industrial chemicals. For these classes of compounds, the primary driver for partitioning behavior of a chemical is its hydrophobicity, or lipophilicity, and most of the relationships explicitly relate the distribution coefficient to the organic carbon content of the solid.
The assumption is that the partitioning of the chemical will be predominantly onto the organic fraction of the solid. While this assumption is useful when dealing with neutral, hydrophobic compounds, for large, multi-functional ionic compounds such as many APIs, the partitioning behavior is more complex.

Cunningham (Cunningham, V. L., 2004) has developed a methodology for calculating partition coefficient (Kp) values for APIs that adsorb to organic solids in wastewater treatment plants (WWTPs). This method uses the K_{OW} or D_{OW} of an API, and its acidic or basic properties to calculate the compound's K_p value. The wastes disposed of in an MSW landfill contain a large fraction of organic solids, that will act as an adsorbent in a way that is similar to the organic content of the primary solids and biological solids in a WWTP. Therefore, landfills have a significant potential for adsorption of organic chemicals, including ionic and neutral APIs, and the K_p values derived by Cunningham are an appropriate basis for estimating the partitioning of APIs to the solids contained in landfills.

The K_p value for an API is used to calculate its concentration in landfill leachate, based on the assumption that equilibrium occurs between the solid and aqueous phases in a landfill. Given that leachate volumes are low compared to the mass of solids present in a landfill , the equilibrium assumption is realistic.

There are sufficient data available in the technical literature on API chemical properties to calculate K_p values for the 24 example APIs. Table 2 presents the calculated K_p values and related physical and chemical characteristics for each of the 24 APIs evaluated in this study. The greater the magnitude of log K_p, the greater is the propensity of the API to adsorb to solid organic and inorganic materials in a landfill.

Calculation of Leachate API Concentrations

The methodology assumes that APIs disposed of in landfills are unpackaged and immediately available for dissolution in the liquid phase. This is a conservative assumption because typically the consumer products will be put in the trash in their packaging. This packaging, which includes plastic bottles and vials, bubble packs, and similar plastic packaging would generally not degrade during the period when the landfill is actively generating leachate (i.e., before it is closed and capped). Therefore, only the amount of API that is present in broken packaging or disposed of without packaging would likely be available for dissolution in the leachate.

The concentration of each API in landfill leachate is calculated using the K_P values in Table 2, which are also included in Table 3. The leachate concentration is adjusted to account for hydrolysis and anaerobic biodegradation that occurs in the landfill. Anaerobic biodegradation fractions are available for three of the 24 example APIs: ibuprofen, trimethoprin, and erythromycin.

Table 2. Partitioning Coefficients for APIs Evaluated

Compound	Dow or Kow	pKa	Functional Group	Log Kp (Ref.1)	Notes
Acetaminophen	7.76	9.5	neutral	0.003	phenol- pKa=9.5; Log D from PALLAS; Log Kp from log(0.531*10^(LogKow-3.21) Barton, DA, McKeown, JJ, Environ. Prog. 10 (2) 96-103
Albuterol Sulfate	0.001	9.3, 10.3	base	0.400	GSK; Dow at pH 7
Cimetidine	1.58	6.9	base	2.319	GSK; Dow at pH 7 pKa=6.9
Ciprofloxacin	0.003	6.09, 8.74	zwitterion	-1.846	From HSDB - Dissociation Constants: pKa = 6.09 (carboxylic acid group); pKa = 8.74 (nitrogen on piperazinyl ring) [Torniainen K et al; Int J Pharm 132: 53-61 (1996)]; Octanol/Water Partition Coefficient: log Kow = 0.28 (non-ionized) [Takacs-Novak,K et al; Int J Pharm 79: 89-96 (1992)]
Codeine	0.003	10.6	base	0.686	HSDB - Dissociation Constants: pKa= 10.60 [Lide, D.R. (ed.). CRC Handbook of Chemistry and Physics. 79th ed. Boca Raton, FL: CRC Press Inc., 1998-1999.,p. 8-56]; log Kow= 1.14 [Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995. 157]
Digoxin	18.1	na	neutral	0.006	HSDB - log Kow = 1.26 [Sangster J; LOGKOW Databank. Sangster Res. Lab., Montreal Quebec, Canada (1994)];Log Kp from log(0.531*10^(LogKow-3.21) Barton, DA, McKeown, JJ, Environ. Prog. 10 (2) 96-103
Diltiazem	23.1	8.41	base	3.018	Log Dow Merck; pka=8.41 (PALLAS)
Doxycycline	0.0537	5.84, 8.23	neutral	0.00002	Log Dow at pH 7 = -1.27 PALLAS; amine pKa=5.84; phenol pKa=8.23. Compound is a zwitterion and will be only about 10% in zwitterion ion form at pH 7; consider as neutral
Enalaprilat	0.079	1.8, 10.63	zwitterion	-1.017	Log Dow, pKas PALLAS
Erythromycin-H2O	66.07	8.8	base	3.292	Log Dow=1.82; pKa = 8.8 (PALLAS)
Fluoxetine	61.9	8.7	base	3.275	secondary amine; Eli Lilly; Dow at pH 7
Gemfibrozil	1.48	4.7	acid	0.500	Pfizer Log Kow=2.47; Dow calculated from Dow=Kow/(1+10^abs(pH-pKa)) whre pH=7
Ibuprofen	1.07	4.4	acid	0.436	Log Dow=1.07 at pH 7.4 [LaRotonda, M.I., Amato, G., Barbato, F., Silipo, C., Vittoria, A. (1983) Quant. Struct. Act. Relat. 2, 168-173]
Lincomycin	3.3	7.6	base	2.511	Merck 5328
Metformin	0.056	12.4	base	1.449	BMS Dow and pKa
Norfloxacin	0.004	6.34,8.75	zwitterion	-1.773	Log Dow = -2.36 pKas PALLAS;
Oxytetracycline	0.0105	8.11	base	1.013	Log Dow=-1.98, pKa = 8.11 PALLAS
Paroxetine metabolite	21.1	9.6	base	2.995	GSK; Dow at pH 7
Ranitidine	0.0815	8.29	base	1.547	GSK; Dow at pH 7; pKas of 8.2 and 2.7;
Sulfamethoxazole	7.76	5.45	base	2.734	Merck pKa
Sulfathiazole	0.372	7.2	base	1.942	log Dow= -0.43; log Kow = 0.05 - [Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995. 55]; pKa= 7.2 - [Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996. 1529];
Tetracycline	0.037	3.3, 8.3,10.2	base	1.342	log Dow = -1.43 (pH 7) -[Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995, 176]. pKas = 3.30, 8.3 and 10.2 as 50% sol in DMF water; [Serjeant EP, Dempsey B; Ionisation constants of organic acids in aqueous solution. IUPAC Chem Data Ser No.23. NY,NY: Pergamon pp. 989 (1979) 77]
Trimethoprim	4.3	6.6, 7.12	base	2.580	log Dow = 0.64 ; log Kow 0.91 [Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995. 124]; pKa = 7.12 - [Perrin DD; Dissociation Constants of Organic Bases in Aqueous Solution. London, UK: Butterworth (1965)];
Warfarin	29	na	acid	1.091	4-hydroxy pyron acidic group- pKa = 4.54 -Pallas; log Dow = 1.46 pH 7 [Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995, 161].
Reference 1: Cunningham, V.L., 2004					
HSDB = Hazarrdous Substance Data Bank, TOXLINE (toxnet.nlm.nih.gov)					
PALLAS 3.0 - Compudrug					

Hydrolysis fractions are available for tetracycline and oxytetracycline. Table 3 presents these fractions as well as the values of log K_p for each API. All of the other APIs were assumed to be unaffected by biodegradation and hydrolysis in the landfill, which is a conservative assumption.

Table 3. Degradation Pathways of APIs Evaluated

Compound	Log Kp	Loss by Human Metabolism (%)	Human Metabolism Reference	Primary and Secondary POTW Removal (%)	POTW Removal Reference	Landfill Anaerobic Biodegradation (fraction remaining)	Landfill Hydrolysis (fraction remaining)
Acetaminophen	0.0025	10	2	98	1	0.0100	1.0000
Albuterol Sulfate	0.4000	72	3	0		1.0000	1.0000
Cimetidine	2.3192	52	2	70	1	1.0000	1.0000
Ciprofloxacin	-1.8457	11	4	74	10,11,12	1.0000	0.0100
Codeine	0.6863	10	8	46	13	1.0000	1.0000
Digoxin	0.0059	16	5	0		1.0000	0.0100
Diltiazem	3.0182	96	2	70	1	1.0000	1.0000
Doxycycline	0.0000	0		0		1.0000	1.0000
Enalaprilat	-1.0173	10	2	30	1	1.0000	1.0000
Erythromycin-H2O	3.2920	0		66	14	1.0000	1.0000
Fluoxetine	3.2750	90	2	85	1	1.0000	1.0000
Gemfibrozil	0.5001	24	2	44	1	1.0000	1.0000
Ibuprofen	0.4356	78	2	90	1	1.0000	1.0000
Lincomycin	2.5111	0		0	11	1.0000	1.0000
Metformin	1.4489	0		7	1	1.0000	1.0000
Norfloxacin	-1.7729	7	2	81	11,12	1.0000	1.0000
Oxytetracycline	1.0127	0		0		1.0000	1.0000
Paroxetine metabolite	2.9946	0		89	1	1.0000	1.0000
Ranitidine	1.5467	6	2	30	1	1.0000	1.0000
Sulfamethoxazole	2.7339	88	7	24	11	1.0000	1.0000
Sulfathiazole	1.9420	15	7	80		1.0000	1.0000
Tetracycline	1.3420	0		0	14	1.0000	1.0000
Trimethoprim	2.5801	15	9	29	1	0.0010	1.0000
Warfarin	1.0906	92	6	0		0.0100	1.0000

(1) "Human Pharmaceuticals: Assessing the Impacts to Aquatic Ecosystems", 2005, SETAC Press, Pensacola, FL, 71-110
(2) PDR* entry for Proventil brand of albuterol, USP
(3) PDR entry for CIPRO IV (ciprofloxacin)
(4) PDR entry for LANOOXICAPS brand of digoxin
(5) PDR entry for COUMADIN Tables
(6) Ruggy, G.H., A Review of the Problem of Sulfonamide Chemotherapy
https://kb.osu.edu/dspace/bitstream/1811/3473/1/V45N03_115.pdf.
(7) Vree, T.B., van der Ven, A.J.A.M., Verwey-van Eissen, C.P.W.G.M., van Ewijk-Beneken Kolmer, E.W.J., Swolfs, A.E.M., van Galen, P.M., Amatdjais-Groenen, H., Isolation, identification and determination of sulfamthoxazole and its known metabolites in human plasma and urine by high-performance liquid chromatography, J. Chromatogr. B, 658 (1004), 327-340
(8) PDR entry for TYLENON with Codeine
(9) Rxlist entry for trimethoprim (Rxlist.com)
(10) "Behavior of Fluoroquinolones and Trimethoprim during Mechanical, Chemical, and Active Sludge Treatment of Sewage Water and Digestion of Sludge," Env.Sci.Technol., 40, 2006
(11) "Removal of Pharmaceuticals in Sewage Treatment Plants in Italy," Env.Sci.Technol., 40, 2006.
(12) "Environmental Exposure and Risk Assessment of Fluoroquinolone Antibacterial Agents in Wastewater and River Water of the Glatt Valley Watershed, Switzerland," Env.Sci.Technol., 36:17, 2002.
(13) "Pilot survey monitoring pharmaceuticals and related compounds in a sewage treatment plant located on the Mediterranean coast," Chemosphere, 66, 2007.
(14) "Occurrence of antibiotics in wastewater treatment facilities in Wisconsin, USA," Sci. Total Env., 36:1, 2006.
*PDR® - Physicians' Desk Reference (electronic version), Thomson Micromedex, Greenswood Village, Colorado, 2002-2006

Table 3 also includes the fractions of each example API that are metabolized by patients that use the medicines and the removal fractions in wastewater treatment plants. If no metabolism data are available for an API, metabolism is assumed to be zero. These data are used for the estimation of releases of APIs to surface waters following treatment of domestic sewage and landfill leachate.

Leachate Volume and API Mass Releases

The leachate volume is calculated from the quantities presented in Table 5-7 of an EPA report on landfill waste containment systems (EPA, December 2002). The maximum volume of leachate generated during the active operation periods of landfills in the northeast and southeast U.S. was used in the calculation. Leachate rates from the northeast and southeast represent the highest leachate rates in the U.S. and were selected to be conservative. The maximum leachate volume, which was used for all leachate calculations in this study, is 14,300 litres per day per hectare (L/ha-day) of landfill surface area. As described in the EPA report, the volume of leachate decreases dramatically once a landfill cell is closed, so use of this maximum leachate volume estimate is highly conservative.

The MSW solids disposal rate is calculated from reported landfill disposal for the years 2003, 2004, and 2005 (EPA, October 2006). The disposal rate used in this study is 2.49 lb/day-person (assuming 29.1% average recycle of MSW, as recorded by EPA). It is also assumed that waste is applied in a 2.5-metre lift per day and at a compacted density of 1,200 lb/yd3 is achieved in the landfill (O'Leary, P. and Walsh, P.W., 1995). These figures represent averages of national data for MSW landfills.

Based on the above assumptions, the rate of leachate generation is calculated as 0.0155 litres/day-capita. For comparison, the average rate of leachate generation for the NE and SE U.S. landfills reported by EPA is 0.0035 litres/day-capita. Use of the maximum leachate generation rate results in a conservative estimate of API leachate mass.

The U.S. population is assumed to be 300,000,000 for the leachate generation calculation. Thus, a total volume of leachate of 1,700,000,000 litres/year is used to estimate the total mass of each API that is leached from MSW landfills. The mass is calculated by multiplying the leachate concentration by the annual leachate volume.

The materials disposed of in MSW landfills constitute a heterogenous matrix, in terms of both the size of the solids and the composition of organic and inorganic materials. Landfills are incompletely saturated (i.e., all voids are not filled with water) and thus not all solids in the landfill are in contact with leachate at any specific time. Therefore, the partitioning of the APIs to solids in an MSW landfill may not be as efficient as the partitioning that would occur in a biological treatment plant.

To account for this heterogeneity, an additional term, referred to in this study as MSW sorption efficiency, was included in the calculation of the API leachate concentration. A range of MSW sorption efficiency from 0.1 to 1.0 was examined to evaluate the sensitivity of the predicted leachate API concentrations and masses to the sorption efficiency in the landfill. An MSW sorption efficiency of 1.0 means that the sorptive efficiency in an MSW landfill is equal to that of the solids in a wastewater treatment plant; a sorptive capacity of 0.1 means that the sorptive efficiency in a landfill is 10% of that in treatment plant solids.

Predicted Surface Water Releases of Leachate

Leachate from Subtitle D landfills is treated at on-site wastewater treatment facilities or at publicly owned treatment works (POTWs). POTWs must achieve a minimum of secondary treatment standards as promulgated at 40 CFR 133 and this study assumed that API removals achieved by conventional secondary treatment would be achieved for APIs in leachate. Many POTWs must apply advanced biological treatment (e.g., nitrification, denitrification) or tertiary treatment (e.g., filtration) to achieve water quality-based effluent limits, so the assumption that all APIs in domestic sewage receive secondary treatment is a conservatively low estimate of removal.

Direct discharges to surface water of treated leachate from Subtitle D landfills must achieve the effluent limitations guidelines at 40 CFR 445, Subpart B. These effluent limitations guidelines are based on best practicable control technology (BPT) for conventional pollutants such as biochemical oxygen demand and total suspended solids, and best available technology economically achievable (BAT) for toxic and non-conventional pollutants. BPT is equivalent to secondary treatment for POTWs, and BAT for Subpart B landfills (Subtitle D in RCRA terminology) is the same as BPT. Therefore, it was assumed for this study that privately owned treatment plants for Subtitle D landfill leachate would achieve the same API fractional removals that are achieved by POTWs. This is also a conservative assumption, because treatment systems that are designed and operated to treat landfill leachate would be expected to achieve higher removals of pollutants than a POTW because the biomass in the treatment system will acclimate to the specific wastewater composition being treated.

To estimate the concentration of each of the example APIs that could enter the environment due to the collection and discharge of leachate, the mass of API discharged after wastewater treatment was calculated using the POTW percent removal data available in the literature. The primary and secondary treatment system removal efficiencies assumed in this study are shown in Table 3.

Contributions by Patient Use

To place the estimated releases of APIs in landfill leachate to surface waters in perspective, the releases of APIs due to patient use and subsequent excretion into domestic sewage was calculated for comparison. The methodology used to calculate surface water releases of APIs is described in Anderson, et al. (2004). The methodology uses the total annual sales of a specific API and calculates a quantity excreted to sewage by patients based on the fraction of the API that is metabolized. The calculated API loading in the sewage is then adjusted for removal in the primary and secondary treatment processes that are typically used at POTWs (Table 3). The quantity of API released to surface waters in the treated sewage is that which remains after accounting for metabolism by patients and treatment at the POTW. The POTW percent removals used for this calculation are the same as those used to calculate the removals of APIs in landfill leachate that is sent to POTWs or privately owned treatment plants for treatment.

Groundwater Releases

The EPA regulations for Subtitle D landfills (40 CFR 258) establish minimum technology guidelines (MTG) for landfill cells constructed after the effective date of the rule. The MTG for landfill liner systems consists of a permeable leachate collection and removal layer (a minimum 12-inch thickness of granular material), located on top of a composite liner consisting of a low permeability geomembrane on top of a minimum 24-inch thickness of compacted, low-permeability clay. These composite liner systems are designed to be highly effective at preventing leachate migration to groundwater.

An EPA study (December 2002) of the performance of Subtitle D landfill liner systems concludes that the required liner systems will substantially prevent leachate migration of the entire period of significant leachate generation for typical landfills. Therefore, for the objectives of this study it was concluded that the landfill-leachate-ground water release pathway is negligible and no estimates of such releases are practical.

RESULTS

The estimated releases to surface water of APIs in landfill leachate, for the 24 example APIs, are shown in Table 4 for one of the three disposal scenarios. Table 4 presents the leachate mass loadings to surface water for three API disposal scenarios – 5%, 10%, and 15% of total annual quantity sold that is discarded unused to landfills — and compares the landfill leachate loadings in treated effluents to the total amount of each API released to surface waters after patient use and wastewater treatment. The assumed MSW sorption efficiency is 0.5.

The APIs shown in Table 4 with the highest potential mass releases to surface water through the landfill leachate pathway are those with low partitioning coefficients (log K_P <1.0), zero anaerobic biodegradation and hydrolysis data for landfills, and minimal or no removal at a POTW.

The estimated leachate release to surface water of acetaminophen, which has the largest sales of any of the 24 example APIs, is very low because although this API has a very low log K_P, it's mass in leachate is predicted to be reduced substantially by anaerobic biodegradation in an MSW landfill and the quantity remaining in the leachate is very effectively biodegraded in the leachate treatment step.

Ibuprofen has relatively high POTW removal (90%), but is sold in very large quantities, has a moderately low K_p, and has no data for anaerobic biodegradation or hydrolysis in landfills. It is significantly metabolized by patients (70%), and therefore the proportion of ibuprofen in the discharge to surface water that originates from unused medicine disposal in landfills is higher than that of acetaminophen.

Table 4 also compares the annual API mass released to surface water through landfill disposal to the total mass of API released to surface water from patient use. Even at the greatest assumed disposal rate of unused medicines in landfills, the landfill leachate pathway to surface water is dwarfed by the surface water releases due to patient use and excretion of the 24 example APIs.

The sensitivity of the leachate API mass discharged to surface water (after POTW treatment) to the MSW sorption efficiency and the quantity of unused medicines disposed of in landfills is shown graphically in Figure 1. A ten-fold decrease in MSW sorption efficiency results in about a 7.5-fold increase in the leachate API mass discharged to surface water. This analysis indicates that the sensitivity of the leachate API mass to the sorption efficiency of the materials in the landfill is less than one to one. As expected, the total mass of API in the leachate is a linear function of the quantity of API disposed of with municipal trash.

Table 4. Impact of Landfill Disposal on Total Surface Water Load of Selected Pharmaceutical Active Ingredients Due to Patient Dosing (0.5 Sorption Efficiency)

Compound	API Qt (kg/year)	Loss by Human Metabolism (%)	POTW Removal (%)*	5% API Disposed			10% API Disposed			15% API Disposed		
				API mass in POTW Effluent due to Patient Use (kg/yr)	API Mass in POTW Effluent from Unused Medicine in Landfills (kg/yr)	Percent of Total Load Resulting from Landfill Disposal	API mass in POTW Effluent due to Patient Use (kg/yr)	API Mass in POTW Effluent from Unused Medicine in Landfills (kg/yr)	Percent of Total Load Resulting from Landfill Disposal	API mass in POTW Effluent due to Patient Use (kg/yr)	API Mass in POTW Effluent from Unused Medicine in Landfills (kg/yr)	Percent of Total Load Resulting from Landfill Disposal
Acetaminophen	5691120	10	98	97318	0.640	0.0007	92196	1.280	0.0014	87074	1.920	0.0022
Albuterol Sulfate	3569	72	0	949	0.809	0.0851	899	1.618	0.1796	849	2.427	0.2849
Cimetidine	49980	52	70	6837	0.041	0.0006	6477	0.082	0.0013	6118	0.123	0.0020
Ciprofloxacin	85440	11	74	18782	11.107	0.0591	17794	22.214	0.1247	16805	33.321	0.1979
Codeine	15095	10	46	6969	0.958	0.0137	6603	1.916	0.0290	6236	2.874	0.0461
Digoxin	229	16	0	183	0.001	0.0007	173	0.003	0.0015	164	0.004	0.0023
Diltiazem	149296	96	70	1702	0.025	0.0014	1612	0.049	0.0030	1523	0.074	0.0048
Doxycycline	32784	0	0	31145	18.540	0.0595	29506	37.079	0.1255	27866	55.619	0.1992
Enalaprilat	772	10	30	462	27.012	5.5249	438	54.024	10.9890	413	81.036	16.3934
Erythromycin-H2O	64283	0	66	20763	0.006	0.0000	19671	0.013	0.0001	18578	0.019	0.0001
Fluoxetine	12434	90	85	177	0.001	0.0003	168	0.001	0.0007	159	0.002	0.0011
Gemfibrozil	231530	24	44	93612	23.365	0.0250	88685	46.729	0.0527	83758	70.094	0.0836
Ibuprofen	1035229	78	90	21636	21.630	0.0999	20498	43.260	0.2106	19359	64.890	0.3341
Lincomycin	328	0	0	312	0.001	0.0002	296	0.001	0.0004	279	0.002	0.0006
Metformin	1597887	0	7	1411733	30.223	0.0021	1337431	60.446	0.0045	1263130	90.669	0.0072
Norfloxacin	2700	7	81	453	25.650	5.3562	429	51.300	10.6724	406	76.950	15.9490
Oxytetracycline	31	0	0	30	0.002	0.0058	28	0.003	0.0123	27	0.005	0.0196
Paroxetine metabolite	19474	0	89	2035	0.001	0.0001	1928	0.002	0.0001	1821	0.004	0.0002
Ranitidine	100417	6	30	62770	1.141	0.0018	59467	2.283	0.0038	56163	3.424	0.0061
Sulfamethoxazole	314389	88	24	27239	0.252	0.0009	25805	0.504	0.0020	24371	0.757	0.0031
Sulfathiazole	483	15	80	78	0.001	0.0008	74	0.001	0.0017	70	0.002	0.0027
Tetracycline	68569	0	0	65141	1.784	0.0027	61712	3.567	0.0058	58284	5.351	0.0092
Trimethoprim	64450	15	29	36951	0.000	0.0000	35006	0.000	0.0000	33061	0.000	0.0000
Warfarin	3999	92	0	304	0.002	0.0006	288	0.004	0.0013	272	0.006	0.0020
Aggregate				1907583	163	0.0086	1807184	326	0.0181	1706785	490	0.0287

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(3) PDR entry for CIPRO IV (ciprofloxacin)
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(9) Rxlist entry for trimethoprim (Rxlist.com)
*PDR® - Physicians’ Desk Reference (electronic version), Thomson Micromedex, Greenswood Village, Colorado, 2002-2006

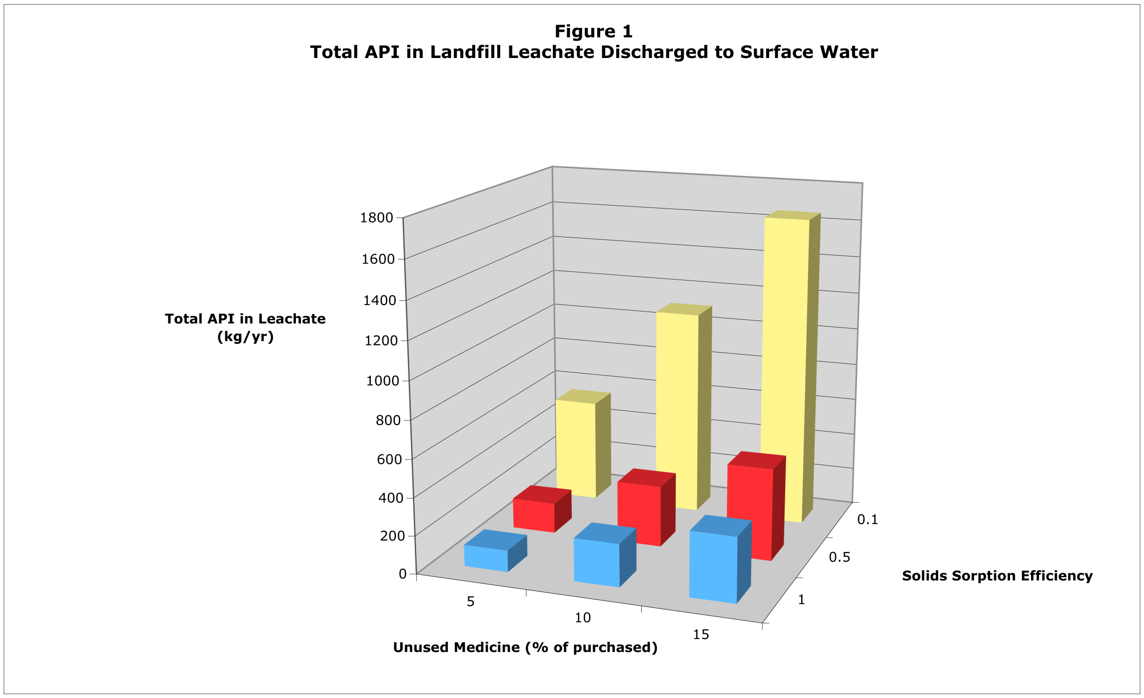

Figure 1. Total API in Landfill Leachate Discharged to Surface Water

Disposal of unused medicines by flushing them to public sewerage systems has been a historically recommended practice. It is useful to compare the disposal of unused medicines by landfill to flushing to the sewer to compare the relative surface water contributions of the two disposal methods.

For this comparison, the estimated aggregate annual surface water releases of the 24 example APIs were calculated by assuming that all unused medicines were disposed of in public sewerage systems. The total surface water release in this calculation is a result of patient use and excretion and disposal of unused medicines to the sewerage systems. The surface water discharge estimates are calculated using the methodology described for landfills (POTW treatment). All API mass quantities are adjusted, as appropriate, to account for the salt fraction of the product if the product is distributed as a salt. The discharges from POTWs due to patient use are based on the mass of API sold, the percentage metabolized, and the percent removed by POTW treatment.

Table 5 presents the calculated surface water discharges of the 24 example APIs assuming unused medicine disposal rates of 5%, 10%, and 15% of annual purchases and a 0.5 sorption efficiency. The percent difference in the total annual surface water discharge of the 24 example APIs that would be caused by unused medicine disposal in sewers, using landfill disposal of unused medicines as the base case for comparison, is 12.6 percent, 20.2 percent, and 28.6 percent for the 5, 10, and 15 percent disposal rates, respectively. This analysis indicates that encouraging the disposal of unused medications in municipal solid waste landfills will decrease the surface discharges of APIs that are caused by this unused medicine disposal.

Table 5. Impact of Unused Medicine Disposal Method on Total Surface Water Load of Selected Pharmaceutical Active Ingredients

Compound	5% Unused Medicine				10% Unused Medicine				15% Unused Medicine			
	API mass in Treated Effluent (kg/yr)-landfill*	API mass in Treated Effluent (kg/yr)-sewer*	Annual Difference (kg)	Annual Percent Difference	API mass in Treated Effluent (kg/yr)-landfill*	API mass in Treated Effluent (kg/yr)-sewer*	Annual Difference (kg)	Annual Percent Difference	API mass in Treated Effluent (kg/yr)-landfill*	API mass in Treated Effluent (kg/yr)-sewer*	Annual Difference (kg)	Annual Percent Difference
Acetaminophen	97319	103009	5690	5.85	97319	103578	6259	6.43	97320	104147	6827	7.02
Albuterol Sulfate	950	1128	178	18.70	951	1256	305	32.11	952	1385	433	45.49
Cimetidine	6837	7587	750	10.96	6837	7977	1139	16.67	6837	8367	1529	22.37
Ciprofloxacin	18793	76511	57718	307.12	18804	76981	58177	309.38	18816	77451	58636	311.63
Codeine	6970	13661	6691	95.99	6971	13737	6765	97.04	6972	13812	6840	98.10
Digoxin	183	194	11	6.26	183	196	13	7.27	183	198	15	8.27
Diltiazem	1702	3941	2239	131.58	1702	6091	4389	257.88	1702	8241	6539	384.19
Doxycycline	31163	32784	1621	5.20	31182	32784	1602	5.14	31200	32784	1584	5.08
Enalaprilat	489	489	0	0.00	516	492	-24	-4.71	543	494	-49	-8.96
Erythromycin-H2O	20763	64283	43520	209.60	20763	64283	43520	209.60	20763	64283	43520	209.60
Fluoxetine	177	270	93	52.63	177	354	177	100.00	177	438	261	147.37
Gemfibrozil	93636	100095	6459	6.90	93659	101651	7992	8.53	93682	103207	9525	10.17
Ibuprofen	21658	26812	5155	23.80	21680	30850	9170	42.30	21701	34887	13186	60.76
Lincomycin	312	328	16	5.26	312	328	16	5.26	312	328	16	5.26
Metformin	1411763	1486035	74272	5.26	1411794	1486035	74241	5.26	1411824	1486035	74211	5.26
Norfloxacin	479	2520	2042	426.32	505	2530	2025	401.43	530	2539	2009	378.96
Oxytetracycline	30	31	2	5.26	30	31	2	5.25	30	31	2	5.24
Paroxetine metabolite	2035	2142	107	5.26	2035	2142	107	5.26	2035	2142	107	5.26
Ranitidine	62772	66285	3513	5.60	62773	66496	3723	5.93	62774	66707	3933	6.27
Sulfamethoxazole	27239	51560	24321	89.29	27239	65393	38154	140.07	27239	79226	51987	190.85
Sulfathiazole	78	414	336	430.96	78	418	340	435.60	78	421	343	440.23
Tetracycline	65143	68569	3427	5.26	65145	68569	3425	5.26	65146	68569	3423	5.25
Trimethoprim	36951	39239	2288	6.19	36951	39582	2631	7.12	36951	39925	2974	8.05
Warfarin	304	504	200	65.79	304	688	384	126.31	304	872	568	186.84
Aggregate	1907746	2148394	240648	12.61	1807510	2172443	364933	20.19	1707274	2196492	489217	28.65

*Includes API contribution from patient use and excretion

Figure 2 compares the surface water discharges of the 24 APIs that were evaluated for three cases: (1) all unused medicine disposal is by flushing to the sewer; (2) all unused medicine disposal is to municipal solid waste landfills; and (3) unused medicine is disposed of elsewhere (i.e., not flushed to the sewer or sent to a landfill) and surface water releases are solely due to patient use.

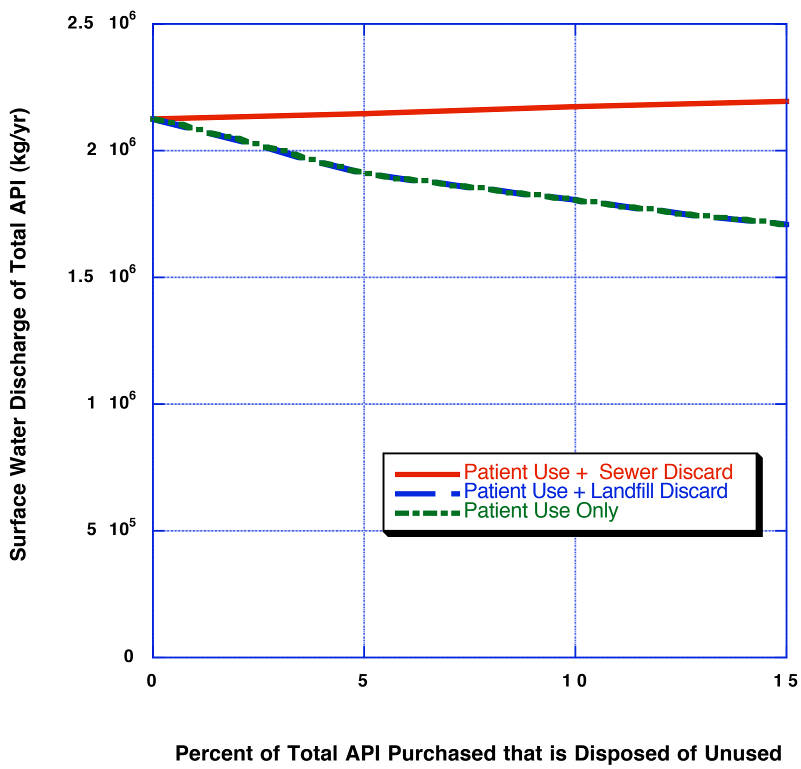

Figure 2. Comparison of Surface Water Discharges from Landfill and Sewer Disposal of Unused Medicines (0.5 Sorption Efficiency)

These are the boundary cases for unused medicine disposal (i.e., 100 % of unused medicines going to one or the other disposal route, not split between both). The quantities of unused medicines are based on three percentages of total annual sales (in kilograms) for each of the 24 APIs evaluated. The contribution of patient use of the medicines, with unused medicines disposed of elsewhere, is also shown on Figure 2 for comparison. As shown, if unused medicines are disposed of in landfills the total surface water contribution is essentially the same as the contribution from patient use alone.

DISCUSSION

There are currently two principal methods that patients can use to dispose of unused medicines: (1) flushing them down the toilet; or (2) disposing of them with household trash. The relative importance of the two disposal methods for unused medicines to total surface water discharges of the 24 example APIs is shown in Table 6. The comparison of the calculated mass discharges is presented in Table 7.

Table 6. Relative Importance of Sewer Flushing and Landfill Disposal of Unused Medicines (0.5 MSW Sorption Efficiency)

Unused Medicine Disposal Method	Percent of Total Surface Water Release due to Specified Disposal Method of Unused Medicines*		
	5% Unused	10% Unused	15% Unused
Sewer Flushing	6.1	12.0	17.8
Landfill	0.01	0.02	0.03

*Includes API contribution from patient use and excretion

The landfill contribution to surface water from unused medicines is calculated by accounting for partitioning of each API to the organic and inorganic solids in the landfill and aerobic and/or anaerobic biodegradation of the API in the landfill, if applicable. It is assumed that the leachate is transferred to a POTW for treatment or treated and discharged at the landfill site. In either case, the POTW treatment efficiencies for each API are applied to calculate the contribution of landfills to surface water discharges. The surface water contribution of unused APIs due to flushing to the sewer is calculated by assuming that the unused mass of API is discharged to the sewer without any metabolism of the chemical. The unused API contribution to the surface discharge is calculated as the mass of unused medicine at each percentage disposal rate multiplied by its percent removal at the POTW.

As shown in Table 6, if unused medicines are flushed to the public sewerage systems such disposal would constitute 6.1%, 12.0%, and 17.8% of the total surface water discharges (including patient use and excretion) for the 5%, 10%, and 15% unused medicine quantities, respectively. The reason why the unused medicine disposal in the sewer causes a larger increment of surface water releases than the unused percentage of total API purchases is that patient use includes metabolism of a number of the APIs before they are excreted, thus reducing the total quantities of those APIs that are sent to the sewer.

Patient use of medicines is the principal source of the surface water discharges of APIs regardless of the disposal method for unused medicines. Landfill attenuation of APIs and subsequent landfill leachate treatment by POTWs or BAT facilities results in substantially lower estimated total discharges of API to surface waters when unused medicines are disposed of by landfilling as opposed to by flushing to the public sewers. There is essentially no difference in the surface water releases of these 24 APIs between the disposal of unused medicines in landfills and disposal of unused medicines elsewhere.

Another way to evaluate the benefits of unused disposal of medicines in landfills as opposed to disposal by flushing them to POTW sewers is to consider the effects of the two disposal methods on the POTW headworks concentrations of the 24 example APIs. The U.S. Food and Drug Administration's (FDA) environmental assessment methodology (for pharmaceuticals uses a total POTW influent flow of 4.431×10^{13} litres per year to estimate potential aquatic impacts of new medicines. Using this annual flow, Table 8 compares the POTW influent concentrations of the 24 example APIs for three cases: (1) patient use only (assuming 5% of medicine is unused but not disposed); (2) patient use plus the contribution of unused medicines flushed to the sewer at a rate of 5% of the total annual use; and (3) patient use plus the contribution from landfill leachate if 5% of unused medicines are landfilled.

Table 8. POTW Headworks Effects of Sewer Flushing and Landfill Disposal of Unused Medicines (0.5 MSW Sorption Efficiency)

Compound	POTW Headworks Concentration (µg/L)		
	Concentration from Patient Use	Concentration w/ 5% of Unused Medicines to Sewer Disposal	Concentration w/ 5% Unused Medicines to Landfill Disposal
Acetaminophen	2.20	2.31	2.20
Albuterol Sulfate	0.02	0.02	0.02
Cimetidine	0.15	0.16	0.15
Ciprofloxacin	1.63	1.71	1.63
Codeine	0.29	0.31	0.29
Digoxin	0.00	0.00	0.00
Diltiazem	0.04	0.04	0.04
Doxycycline	0.70	0.74	0.70
Enalaprilat	0.01	0.01	0.01
Erythromycin-H2O	1.38	1.45	1.38
Fluoxetine	0.00	0.00	0.00
Gemfibrozil	2.11	2.22	2.11
Ibuprofen	0.49	0.51	0.49
Lincomycin	0.01	0.01	0.01
Metformin	31.86	33.45	31.86
Norfloxacin	0.05	0.06	0.05
Oxytetracycline	0.00	0.00	0.00
Paroxetine metabolite	0.05	0.05	0.05
Ranitidine	1.42	1.49	1.42
Sulfamethoxazole	0.81	0.85	0.81
Sulfathiazole	0.01	0.01	0.01
Tetracycline	1.47	1.54	1.47
Trimethoprim	0.83	0.88	0.83
Warfarin	0.01	0.01	0.01
Aggregate	45.55	47.82	45.55

As shown in Table 8, landfill disposal results in reductions in POTW influent concentrations to the extent that they are essentially the same as if the contribution was only due to patient use of the medicines.

CONCLUSIONS

The objective of this study was to estimate the potential releases of APIs to surface water resulting from the disposal of unused medicines in Subtitle D (MSW) landfills. Based on the evaluation performed for 24 APIs, it can be concluded that:

1. If all unused medicines are disposed of in landfills, a very conservative estimate of 99.9% to 99.97% of API surface water releases would be due to patient excretion (at an assumed landfill sorption efficiency of 0.5). The landfill disposal pathway to surface water accounts for an average of 0.01% to 0.03% of the estimated aggregate annual surface water releases for the 24 APIs evaluated by this study. These landfill contributions are based upon conservative assumptions of landfill leachate generation that would tend to predict higher contributions.

2. If all unused medicines were disposed of by flushing to the sewer, then unused medicine disposal would constitute approximately 6.1%, 12.0% and 17.8% of the total surface water discharges of these 24 APIs at 5%, 10%, and 15% rates of unused medicine disposal (as a function of annual sales), respectively.

3. The partitioning efficiency of the 24 example APIs in landfills is relatively insensitive to the heterogeneity of the materials in the landfill, as represented by the efficiency of adsorption of APIs to landfill solids compared to the corresponding sorption to wastewater treatment plant biological solids.

4. This study indicates that encouraging the disposal of unused medications in municipal solid waste landfills will decrease the surface water discharges of APIs that are caused by disposal of unused medicines by flushing to sewerage systems.

5. Based on EPA reports on the integrity of modern MSW landfill liners, the landfill-leachate-ground water release pathway is negligible and no estimates of such releases are practical.

6. These estimated releases of APIs in landfill leachate are calculated for the period of active operation of a landfill. Once the landfill cells are closed and capped, EPA data on containment systems document that leachate volumes are negligible. Therefore, upon landfill cell closure, future releases of APIs will be essentially zero.

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and the study results. This study extends work on landfill disposal of APIs that was performed for PhRMA by Golder Associates (2004).

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